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SYSTEMATIC REVIEW ARTICLE

How to Optimize the Effectiveness and Safety of Parkinson's Disease Therapy? – A Systematic Review of Drugs Interactions with Food and Dietary Supplements

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Abstract: ***Background*:** Despite increasing worldwide incidence of Parkinson's disease, the therapy is still suboptimal due to the diversified clinical manifestations, lack of sufficient treatment, the poor adherence in advanced patients, and varied response. Proper intake of medications regarding food and managing drug-food interactions may optimize Parkinson's disease treatment.

***Objectives*:** We investigated potential effects that food, beverages, and dietary supplements may have on the pharmacokinetics and pharmacodynamics of drugs used by parkinsonian patients; identified the most probable interactions; and shaped recommendations for the optimal intake of drugs regarding food.

***Methods*:** We performed a systematic review in adherence to PRISMA guidelines, and included a total of 81 studies in the qualitative synthesis.

***Results and Conclusion*:** We found evidence for levodopa positive interaction with coffee, fiber and vitamin C, as well as for the potential beneficial impact of low-fat and protein redistribution diet. Contrastingly, high-protein diet and ferrous sulfate supplements can negatively affect levodopa pharmacokinetics and effectiveness. For other drugs, the data of food impact are scarce. Based on the available limited evidence, all dopamine agonists (bromocriptine, cabergoline, ropinirole), tolcapone, rasagiline, selegiline in tablets, safinamide, amantadine and pimavanserin can be taken with or without a meal. Opicapone and orally disintegrating selegiline tablets should be administered on an empty stomach. Of monoamine oxidase B inhibitors, safinamide is the least susceptible for interaction with the tyramine-rich food, whereas selegiline and rasagiline may lose selectivity to monoamine oxidase B when administered in supratherapeutic doses. The level of presented evidence is low due to the poor studies design, their insufficient actuality, and missing data.

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1. INTRODUCTION

Parkinson's disease (PD) is a progressive, neurodegenerative disorder – the second most common after Alzheimer's disease [1]. In the course of PD, the gradual degeneration or loss of dopaminergic neurons occurs, mainly in the substantia nigra. This leads to the deficiency of dopamine - the neurotransmitter involved in the initiation and coordination of movement. As a consequence, patients with PD may experience postural instability, resting tremor (trembling in the jaw, hands, arms, and legs), rigidity (stiffness of the limbs), and bradykinesia (slowing down of movement). Apart from these cardinal motor manifestations of the disease, non-motor symptoms can be observed as well, such as sleep behavior disorders, apathy, depression, cognitive impairment, and constipation [2]. Additionally, it is estimated that even 80% of parkinsonian patients, especially in advanced stages of the disease, may suffer from dysphagia [3]. Swallowing problems can contribute to malnutrition and aspiration pneumonia [4].

Clinical picture of PD is diversified, since the occurrence and severity of the abovementioned symptoms depend on the stage of the disease. PD progression can be assessed using *e.g.* the Hoehn and Yahr 5-degree scale, where 1-3 refers to early stages of PD, with symptoms from mild to moderate, whereas 4 and 5 indicate an advanced stage of disease, with severe patient's disability [5].

During the last 3 decades, the worldwide incidence of PD has more than doubled and is projected to double again by the year 2040 [6, 7]. Still, only long-term symptomatic treatment is available, with dopamine replacement therapy as

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a gold standard [8, 9]. Its primary aim is to overcome dopamine deficiency either by administering drugs that can convert to dopamine (levodopa) or act on post-synaptic dopamine receptors (dopamine agonists). Other groups of drugs, *e.g.* monoamine oxidase B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, and amantadine are regarded as adjunctive treatment [8, 9]. Besides, drugs that target specific symptoms can be considered as well, *e.g.* anticholinergic drugs for tremor, spastic syndrome or salivation, selective serotonin reuptake inhibitors (SSRIs) for depression, pimavanserin for psychosis, or rivastigmine and donepezil for dementia [10].

Nevertheless, adherence to the therapy in patients with advanced PD is often suboptimal. The significant factors contributing to that are older age, concomitant diseases, such as dementia or depression, polypharmacy, the complex therapeutic schedule, and insufficient family support [11].

Another serious challenge in PD treatment is dosing optimization. Dopamine replacement therapy cannot stop the dopaminergic denervation and the gradual loss of neurons affects the efficacy of treatment in a nonlinear manner. Hence, with the progress of the disease, doses of drugs need to be individually adjusted [12].

Optimization of PD therapy appears to be crucial to overcoming limitations, such as the lack of sufficient treatment, poor adherence in advanced patients, and varied response to the therapy. The dosing regimen and drug-food interactions - although often underestimated by patients and health care professionals; can either positively or negatively influence the effectiveness and safety of PD treatment. The risk of interactions increases with the patient's age and number of drugs prescribed [13]. Awareness and education of the proper intake of antiparkinsonian drugs with regard to food and dietary supplements may provide an inexpensive and easy method to optimize the treatment, especially in the elderly population of advanced parkinsonian patients.

The aim of our review was to investigate potential effects that food, beverages, and dietary supplements may have on the pharmacology of the antiparkinsonian drugs, both in the pharmacokinetic and in the pharmacodynamic phase; to identify the most probable interactions; and to shape recommendations for the optimal intake of drugs regarding food.

2. MATERIALS AND METHODS

2.1. Search Strategy

We independently performed a systematic search of the literature in adherence to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statements. The databases examined under the paper were Medline (via PubMed) and Embase, covering reports from 1970 to 2020. We also researched other resources such as Micromedex, drugs.com, AHFS, and UpToDate, as well as product characteristics of the antiparkinsonian drugs. Additional publications were found by checking the reference lists.

To complete the searches, we used keywords and phrases as follows: antiparkinsonian drugs names ("levodopa", "ropinirole", "pramipexole", "apomorphine", "piribedil", "bromocriptine", "cabergoline", "selegiline", "rasagiline", "safinamide", "entacapone", "opicapone", "tolcapone", "trihexyphenidyl", "benztropine", "biperiden", "pridinol", "amantadine", "istradefylline", "pimavanserin") in combinations with "food", "food-drug interaction", "meal", "juice", "coffee", "tea", "fiber", "aspartame", "enteral nutrition", "iron", "protein", "pyridoxine", "tyramine", "vitamin C".

2.2. Inclusion Criteria

All articles describing or assessing the impact of meals, beverages, and dietary supplements on the pharmacokinetic and pharmacodynamic parameters of orally taken antiparkinsonian drugs were considered for inclusion in this systematic review. We made no restrictions for study year, study design, number of participants, or their characteristics.

2.3. Exclusion Criteria

We excluded studies written in a language other than English, not peer-reviewed studies (*e.g.* studies whose results were mentioned only in the product characteristics), in vitro studies, and preclinical studies.

2.4. Data Extraction

We extracted available data of study type, number of participants, participants characteristics (health state, age, disease duration; if applicable, HY stage of disease; if applicable), drug dose and formulation, qualitative and quantitative composition of food, reported outcomes, and possible mechanism of interaction between drug and food.

3. RESULTS AND DISCUSSION

3.1. Eligible Studies

As presented in Fig. (**1**), during the searching process, we independently identified a total of 144 articles based on initial titles and abstracts screening. After removing 6 duplicates, we carefully screened abstracts of 138 studies and excluded 27 articles due to not meeting the inclusion criteria. After assessing 111 full-text articles for eligibility, we further removed 30 articles according to exclusion criteria (4 not written in English, 14 not peer-reviewed, 4 in vitro studies, and 8 preclinical studies). Finally, we included a total of 81 studies in the qualitative synthesis.

3.2. Level of Evidence

Based on the study design, for each of included studies, we defined a level of evidence, with alphabetic designation as follows:

- level A – for randomized clinical studies,
- level B – for non-randomized clinical studies,
- level C – for case-control and cohort studies,
- level D – for cross-sectional studies and case reports.

3.3. Levodopa

Levodopa (L-dopa) is a precursor of dopamine and, unlike dopamine, can cross the blood-brain barrier. However, only approximately 1% of orally taken levodopa reaches the brain due to being rapidly converted into dopamine by peripheral aromatic-L-amino-acid decarboxylases. To inhibit

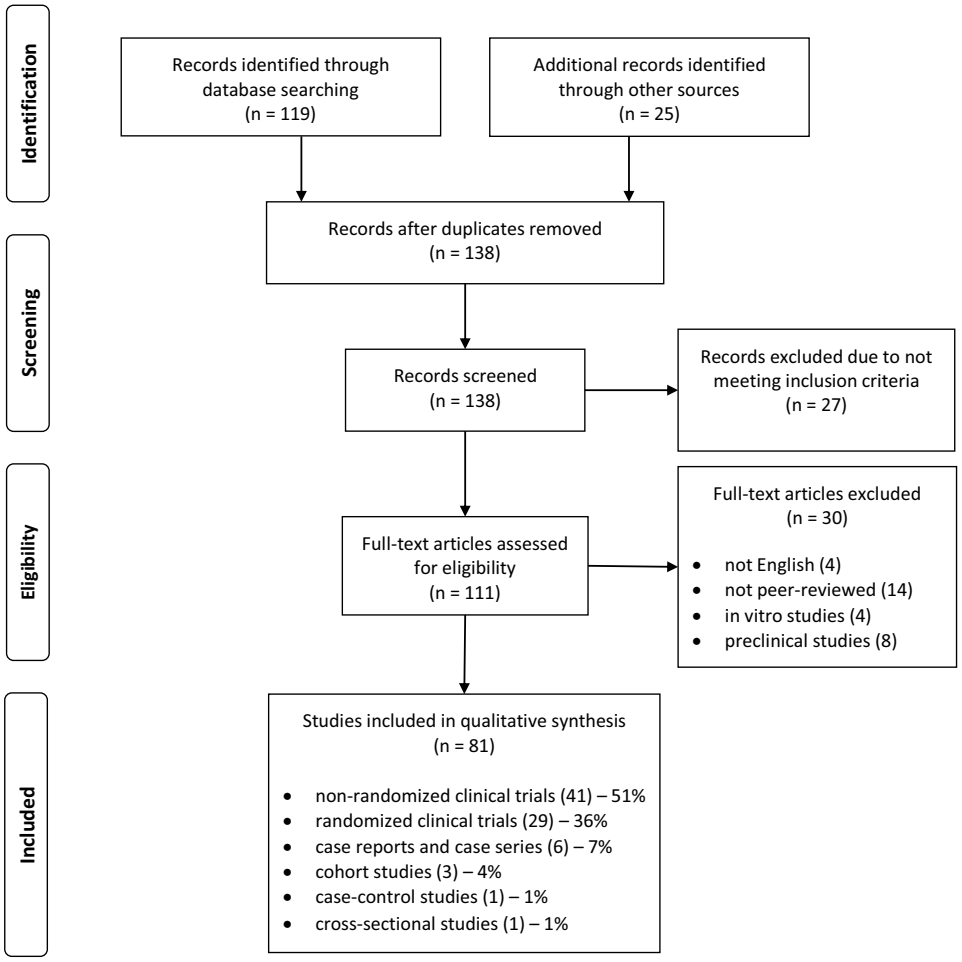

Fig. (1). Flowchart of the searching strategy.

extracerebral metabolism, levodopa is combined with carbidopa or benserazide. It allows lowering both the levodopa dose and the occurrence of peripheral adverse effects. Still, with the progress of the disease, several challenges of levodopa treatment occur, such as wearing off (weaker or shorter response to the dose that was earlier effective) and on-off phenomenon (fluctuations between good and not an adequate response to the given dose). Increasing levodopa dose can improve the clinical response but may also lead to involuntary movements (levodopa-induced dyskinesias, LID) [14].

Another serious problem is that levodopa has a short half-life, so immediate-release (IR) tablets should be taken several times a day. However, even with optimal dosing, drug concentrations can be unstable. To improve patient's adherence and maintain continuous dopaminergic stimulation, modified-release formulations of levodopa + carbidopa / benserazide were developed, *e.g.* controlled-release (CR) tablets, dual-release (DR) tablets, extended-release (ER) capsules, and hydrodynamically balanced system (HBS) [15]. Additionally, dispersible tablets were designed for patients with swallowing difficulties or receiving enteral nutrition.

In several countries, continuous intrajejunal infusion of levodopa-carbidopa intestinal gel (LCIG) via a percutaneous pump was introduced for patients with severe motor fluctuations and dyskinesia [16].

3.3.1. Impact of Food on Different Levodopa Formulations

Various levodopa + carbidopa / benserazide formulations are differently affected by food. In studies of IR tablets, the rate of levodopa absorption was significantly lower after a standard meal: the maximum serum concentration (C_{max}) decreased by 30% and the time to reach C_{max} (t_{max}) was delayed by 0.5-1 h [17, 18]. Delayed gastric emptying in the presence of food can be proposed as the explanation for these results. Contrastingly, the impact of meal on levodopa area under the plasma concentration-time curve (AUC) varied among studies, from 15-27% decrease [17, 18] to even 22% increase [19, 20]. Nevertheless, IR levodopa tablets should be ingested 30-60 minutes before a meal, for a more rapid mode of action [10]. The same recommendation can be made for dispersible tablets [21].

The slower rate of levodopa absorption after food intake was observed for CR tablets [22, 23], DR tablets [24], and ER capsules [25] as well, probably because of the delayed gastric emptying. The presence of meal significantly flattered the concentration-time profile of levodopa CR tablets [22] and delayed time to onset of motor response [23]. Due to not significantly altered levodopa bioavailability, it is not obligatory to take CR, DR, and ER formulations on an empty stomach. However, administration in a constant relationship to food should be recommended [23, 24].

No significant impact of food was reported for hydrodynamically balanced system (HBS) of levodopa; hence this formulation can be ingested irrespectively of meals [19].

During the treatment with levodopa-carbidopa intestinal gel (LCIG), less fluctuations in plasma levodopa concentrations were observed with lunch than while fasting. It was suggested that intake of small amounts of food can be beneficial in patients on LCIG, who experience motor fluctuations in the afternoon [26].

3.3.2. Levodopa and Protein Intake

A high-protein diet correlates with the lower levodopa efficacy. It is manifested by the prematurely terminated response to treatment [27], a decline in motor performance [28-30] and bradykinesia [31, 32]. After the meal rich in protein, plasma large neutral amino acid (LNAA) levels increase [27-29, 33]. Dietary LNAAs, *e.g.* tryptophan, tyrosine, phenylalanine or branched-chain amino acids (BCAA) may compete with levodopa since they are absorbed in the gut and passed through the blood-brain barrier *via* the same saturable transporting system. In several studies, therapy was ineffective after a high-protein meal, although levodopa plasma levels increased relative to the fasting state [28, 29, 32, 33]. Moreover, Simon *et al.* [34] reported that levodopa AUC can be even 42% higher in the presence of high-protein meal (containing 38.7 g of protein). In contrary, Robertson *et al.* [35] found no significant changes in levodopa pharmacokinetic parameters after protein load. Nevertheless, all these studies indicate that levodopa absorption in the gut is not diminished by LNAAs. Hence, the most probable mechanism to explain lower levodopa efficacy in the presence of high-protein meals is the competition with LNAAs, especially BCAA, for the transport through the blood-brain barrier.

By contrast, introducing a low-protein diet (up to 0.8 g/kg/day) resulted in a more potent and stable levodopa mode of action [36]. Relative to fasted conditions, LNAAs levels did not significantly change [27]; however, they were decreased when compared to the high-protein and balanced diets [37-39]. Low protein intake diminished the severity of motor fluctuations, with longer "on" and shorter "off" phases [37-41].

Since protein intake mainly at breakfast and lunch significantly contribute to motor fluctuations, shifting protein consumption to an evening meal may help to maintain PD treatment effectiveness [42]. Such approach; protein redistribution diet (PRD); was found to alleviate parkinsonian symptoms: improve motor performance and lower disability score [31, 33, 43-46]. After introducing PRD, several authors reported dyskinesias and a need to decrease daily levodopa dose due to its more potent action [31, 33, 36]. Some patients with non-respondence to levodopa restored drug sensitivity while on PRD [33, 43]. In studies of patients with on-off fluctuations on PRD, longer "on" and shorter "off" phases were observed [31, 44, 46, 47].

Despite mentioned benefits of protein-restricted diets, its widespread use is still controversial. In a recent retrospective study, only 5.9% of 877 patients reported levodopa interaction with protein; hence, the scope of the problem seems to be relatively small [48]. Moreover, parkinsonian patients are at increased risk of weight loss and malnutrition. For older adults, the suggested reasonable protein intake is approximately 1.5 g/kg/day, which is 2 times higher than recommended in low-protein diets [42]. There are problems with prolonged acceptance and adherence to diets as well [49]. It seems reasonable to introduce protein-restricted diets to parkinsonian patients with motor fluctuations [42, 49]. In the early stage of PD, a low-protein diet can be proposed as the first choice, since it is easier for the patient to adhere [42]. Patients with advanced PD or severe motor fluctuations may obtain benefit from a protein redistribution diet which is likely to be more effective [42].

3.3.3. Levodopa and Enteral Nutrition

Enteral nutrition is often introduced in patients with advanced Parkinsonian disease, due to swallowing problems and malnutrition or after surgical interventions. Several clinical cases reported the negative interaction between continuous enteral nutrition and levodopa [50-52]. All resulted in the loss of drug efficacy, indicated by severe rigidity despite the treatment [51] or the development of neuroleptic malignant-like syndrome [50, 52]. Interactions occurred due to the high amount of protein in enteral nutrition [50]. To avoid interference, such approaches can be proposed: decreasing the protein content in enteral nutrition, separating levodopa administration from enteral nutrition, or increasing levodopa dose [51].

3.3.4. Levodopa and Coffee

According to the recent meta-analysis, regular coffee consumption might be associated with a lower risk of developing Parkinson's disease and the slower rate of progression [53]. Caffeine and other methylxanthines present in coffee may contribute to its protective impact on dopaminergic neurons [54]. Methylxanthines act as non-selective adenosine receptor antagonists. Adenosine receptors subtype A1 and A2A are present in the brain and regulate *e.g.* , motor function, synaptic plasticity, and neuronal signaling. Upregulation of A2A receptors was observed in conditions characterized by neurodegeneration or chronic stress [54]. Moreover, in rats and mice, blocking of A2A receptors prevented synaptotoxicity and reversed memory impairments [55, 56].

The evidence for the impact of coffee on levodopa therapy is conflicting. In the early study of 4 patients, prolonged intake of high caffeine doses (from 300 to 1400 mg) increased the duration of levodopa-induced dyskinesias (LID) [57]. Contrastingly, more recent studies revealed that regular moderate coffee consumption (1-3 cups a day) may negatively correlate with the presence of LID [58, 59]. Deleu *et al.* [60] focused on the effect of 200 mg caffeine on levodopa pharmacokinetics and pharmacodynamics in PD patients. They concluded that caffeine may decrease levodopa t_{max} by 0.5 h and shorten the latency to walking and tapping response (2 and 3 times, respectively). The proposed mechanism to explain these results is that caffeine accelerates gastric emptying, and, in consequence, enhances levodopa absorption [60].

3.3.5. Levodopa and Fiber

About 50 to 80% of PD patients suffer from constipation [61]. This may be due to the delay of the gastrointestinal (GI) transit, decreased bowel motility, and the use of choli-

nolytics. Prokinetic drugs, despite providing relief, cannot be administered chronically due to adverse effects, so the use of fiber is often considered a safer alternative [62]. Fiber increases the volume and weight of stool, makes it softer and easier to pass through the GI tract, and accelerates bowel movements. However, fiber consumption may influence the bioavailability of levodopa. In rats, co-administration of *Plantago ovata* husk (100 or 400 mg/kg) and levodopa (20 mg/kg) resulted in significantly lower values of levodopa C_{max}, slower drug elimination, and increased extent of absorption with higher final levels. These changes directly translate into a lower risk of levodopa side effects and a longer, more stable mode of action [63-65].

Similar results were obtained in a clinical study of PD patients. Although changes in C_{max} after *P. ovata* husk intake with levodopa IR tablets were insignificant, the presence of fiber provided more homogenous and smooth levodopa absorption (with fewer peaks in the concentration-time curve and higher final concentrations) [66]. The earlier clinical study focused on the clinical effects of introducing the fiber-enriched diet in PD patients with constipation. After 2 months, not only the significant increase of levodopa IR tablets bioavailability was observed (by 71%), but also the improvement in GI motility, constipation, and patient's coordination [67].

Several mechanisms were proposed to explain the effects of fiber on levodopa bioavailability. Delaying gastric emptying by fiber may increase levodopa degradation in the stomach and hence contribute to the decrease of C_{max}. Another explanation is that levodopa can be trapped in a viscous solution formed by fiber. In consequence, not only drug absorption may decrease and delay, but the presystemic metabolism as well. Moreover, the presence of fiber may promote paracellular absorption of levodopa, so the higher amount of drug can pass the gut wall without being degraded by aromatic amino acid decarboxylases that are present inside enterocytes [68].

3.3.6. Levodopa and Vitamin C

Vitamin C (syn. ascorbic acid) may exhibit neuroprotective effects due to antioxidant properties. In a mouse model, ascorbic acid protected against acute oxidative toxicity of levodopa and decreased the occurrence of side effects [69].

Clinical study of patients with Parkinson's disease revealed that vitamin C can significantly improve levodopa bioavailability - increase of AUC (by 35%) and C_{max} (by 53%) and decrease of t_{max} (by 38%) were observed – but only in patients with a poor baseline levodopa absorption [70]. The positive ascorbic acid impact can be explained by its lowering of gastric pH – due to acidic properties and stimulation of gastric acid secretion. A more acidic environment promotes levodopa solubility. Additionally, vitamin C may stimulate bowel movements and hence, contribute to faster onset of levodopa action. The results of the study suggest that combining ascorbic acid with levodopa can be a simple strategy to improve the efficacy of PD treatment [70].

3.3.7. Levodopa and Vitamin B6

Vitamin B6 (syn. pyridoxine) activates enzymatic decarboxylation of aromatic L-amino acids and hence can accelerate levodopa metabolism. We found several studies from the early-70s reporting the reduction of dyskinetic side effects after co-administration of levodopa with oral (50-100 mg) or intravenous (10 mg) pyridoxine, but usually with concomitant loss of levodopa efficacy [71-74]. In three studies, decreases of levodopa plasma levels (by 60-67%) in the presence of oral or intramuscular pyridoxine were observed as well [73,75,76]. It should be noted, however, that pyridoxine doses in these studies were much higher than doses taken during the standard supplementation. Moreover, after introducing aromatic-L-amino-acid decarboxylase inhibitors (such as carbidopa) to therapy with levodopa, the negative effect of pyridoxine disappeared [72,77-79]. Nowadays, the vast majority of patients administer fixed-dose formulations of levodopa with carbidopa or benserazide; hence concomitant vitamin B6 supplementation should not affect the efficacy of treatment [80].

Over one-third of PD patients chronically treated with levodopa may develop peripheral neuropathy. Oral levodopa formulations are associated mainly with slowly progressive neuropathy, whereas the acute or subacute onset can be observed predominantly in patients on LCIG [81]. One of the factors contributing to the development of neuropathy is low vitamin B6 level. Additionally, pyridoxine deficiency may accelerate the time to develop levodopa-induced dyskinesias and on-off fluctuations [80]. Loens *et al.* compared the prevalence of vitamin B deficiency in patients treated either with oral levodopa or LCIG. Interestingly, they observed an inverse correlation between pyridoxine plasma levels and levodopa daily dose irrespective of the route of drug administration [82]. In a recent study, pyridoxine deficiency was confirmed in 13 of 18 patients chronically treated with oral levodopa, and for all of 6 patients on LCIG. Similarly, as in the previous study, pyridoxine deficiency correlated with higher levodopa daily doses [80]. Pyridoxine deficiency can be induced either by metabolizing levodopa by pyridoxine or irreversible binding of pyridoxine by carbidopa. Vitamin B6 supplementation should be considered in patients with confirmed deficiency, especially when receiving daily levodopa doses higher than 2000 mg or having levodopa dose rapidly increased in a short time (as it usually happens during the initiation of LCGI). It is recommended, however, to monitor the patient's condition and vitamin B6 level, since high pyridoxine doses (usually above 1000 mg per day) may cause neuropathy as well [82].

3.3.8. Levodopa and Iron Supplements

It is well established that iron can contribute to the pathogenesis of Parkinson's disease *via* ferroptosis - regulated cell death pathway, which is iron-dependent [83, 84]. Despite limited evidence of iron efficacy, some Parkinsonian patients may take iron supplements or multivitamin preparations containing iron as the supportive therapy for anemia or feeling of weakness [85]. We found 2 clinical studies examining the effect of levodopa co-intake with iron in the form of ferrous sulfate [86, 87]. In both of them, levodopa AUC and C_{max} significantly decreased (by 30-51% and 47-55%, respectively) and t_{max} remained unaffected, suggesting impaired drug absorption in the presence of ferrous sulfate. Iron can form chelates with drugs containing a catechol structure (such as levodopa or carbidopa), and it seems to be the most

probable mechanism of this interaction [88]. The interval of 2 h between administration of levodopa and iron salts should be maintained to avoid chelation [89].

3.3.9. Levodopa and Aspartame

Older patients with PD often suffer from concomitant diseases, such as diabetes, hence may use aspartame as the artificial sweetener. In the gut, aspartame is hydrolyzed to one of LNAAs – phenylalanine that may compete with levodopa uptake and decrease drug absorption. We found only one study assessing the clinical outcome of this potential interaction. Levodopa was administered with two doses of aspartame - 600 or 1200 mg. Although ingesting the higher dose resulted in significantly increased levels of phenylalanine, no significant changes were observed in the patient's motor performance. Currently, no evidence is available for the negative impact of aspartame on levodopa efficacy [90].

In Tables **1** and **2**, we present detailed characteristics of studies assessing the impact of food on pharmacokinetics and pharmacodynamics of levodopa in healthy volunteers and parkinsonian patients.

3.4. Dopamine Agonists

Dopamine agonists mimic the effect of dopamine by activating dopaminergic receptors in the brain. Compared to levodopa, dopamine agonists are less effective but rarely cause dyskinesias and on-off fluctuations. We found studies investigating the impact of food on the bioavailability of ropinirole, bromocriptine, and cabergoline. Of these three drugs, cabergoline seems to be the least susceptible for interactions with food: no significant changes in pharmacokinetic parameters were observed [91]. For ropinirole and bromocriptine, the rate of absorption was markedly delayed in the presence of food, however, with no significant impact on overall bioavailability [92-96]. All investigated dopamine agonists can be taken with or without food. Co-intake with meals may be beneficial due to reducing the occurrence of nausea [97, 98].

Bromocriptine is metabolized by cytochrome P450 3A4 - enzyme that can be inhibited by grapefruit juice [99]. Although we did not find any literature evidence, such interaction may theoretically occur. Patients treated with bromocriptine should avoid excessive grapefruit juice consumption.

In patients with gastrointestinal problems, such as heartburn, bloating or dysphagia, oral dopamine agonists can be replaced with rotigotine in transdermal patches. Additionally, this formulation provides steady dopaminergic stimulation over 24-h period and offers convenient, once-daily administration [100].

In Table **3**, we present detailed characteristics of studies assessing the impact of food on pharmacokinetics and pharmacodynamics of dopamine agonists.

3.5. COMT Inhibitors

Levodopa undergoes significant metabolism by catechol-O-methyltransferase (COMT) to inactive metabolites. By inhibiting COMT, less levodopa is degraded in the bloodstream, and thereby more amount of the drug can penetrate through the blood-brain barrier. Various COMT inhibitors, *e.g.*, entacapone, tolcapone, and opicapone, are used in combination with levodopa, to decrease doses and to lower the severity and frequency of motor fluctuations [8,10,14].

We found data on the food impact on the absorption of tolcapone and opicapone. Of note, in some countries, tolcapone is withdrawn from the market due to hepatotoxicity and cases of sudden cardiac deaths [14]. According to prescribing information, food may delay and decrease the tolcapone absorption, but without significant effect on the relative bioavailability [101]. This is in line with the findings of a study using pharmacostatistical models to describe tolcapone pharmacokinetics in patients with PD. The presence of food decreased the relative bioavailability of tolcapone by 10-20%; however, these changes were clinically irrelevant [102]. Tolcapone can be administered with or without food [101].

Contrastingly, moderate- and high-fat meals have a negative impact both on the rate, and the extend of opicapone absorption, causing the significant delay of t_{max}, and the decrease of AUC (by 31-51%) and C_{max} (by 62-68%) [103, 104]. Although the mechanism of interaction was not proposed, we assume that the delay of gastric emptying caused by food can partly explain these results. According to the product characteristics, opicapone should be ingested 1 h before or 1 h after the meal [105].

3.6. MAO-B Inhibitors

Monoamine oxidase B (MAO-B) inhibitors, *e.g.* , selegiline, rasagiline, and safinamide, selectively block MAO-B – an enzyme that metabolizes dopamine and thereby can extend the duration of action of levodopa. These MAO-B inhibitors are used separately or as adjunctive therapy to levodopa [14]. Combined treatment allows to lower levodopa dose and may reduce the wearing-off effect as well. All MAO-B inhibitors are available in oral forms (tablets, orally disintegrating tablets or capsules), and selegiline additionally in transdermal patches [8,14]. The transdermal route was designed to increase the amount of drug delivered to the brain and provide sustained plasma concentrations [106].

3.6.1. Impact of Food

For orally given selegiline, the impact of food depends on the drug formulation. In a study of tablets taken with a high-fat meal, a more than 3-fold increase of selegiline bioavailability was observed [107]. The proposed explanations for enhanced absorption were increases in splanchnic blood flow and delayed stomach emptying after a meal [107]. According to the prescribing information, selegiline tablets should be administered with food [108]. On the other hand, orally disintegrating tablets (ODT) need to be taken 5 minutes before or after the meal, due to the 40% lower AUC and C_{max} in the presence of food [109].

The bioavailability of oral rasagiline and safinamide formulations was investigated after co-intake with the high-fat meal. The presence of food caused the delay of t_{max} (by 25-40 min. for rasagiline and by 0.75-3.3 h for safinamide), and the decrease of C_{max} (by 51-60% and 16%, respectively). Nevertheless, the extent of absorption, measured as AUC,

Table 1. Summary of studies assessing the impact of food on pharmacokinetics and pharmacodynamics of levodopa in healthy volunteers.

Study	Number of Participants	Mean Drug Dose (mg)	Drug Formulation	Type of Meal / Food Ingredient	Meal / Food Ingredient Characteristics	Observed Effect	Level of Evidence
Wilding *et al.* [20]	6	200	tablets *vs.* controlled-release tablets +[a] carbidopa	light meal	358 kcal	tablets: ↑[b] absolute bioavailability by 7% controlled-release tablets: ↑ absolute bioavailability by 12%	level A
Crevoisier *et al.* [24]	19	200	dual-release tablets + benserazide	high-fat meal	1046 kcal, 138 g of carbohydrates, 43 g of fat, 28 g of protein, 3 slices of bread (150 g), 30 g of cheese, 60 g of marmalade, 30 g of butter, 200 mL of whole milk, 10 g of sugar, 100 mL of herbal tea	no significant changes in AUC[c] and $t_{1/2}$[d], ↓[e] C_{max}[f] by 33%, t_{max}[g] delayed by 2 h	level A
Yao *et al.* [25]	21	490	extended-release capsules + carbidopa	high-fat meal, 30 min. before dosing	2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 8 oz of hash brown potatoes, and 8 oz of whole milk	↑AUC by 13%, ↓C_{max} by 21%, t_{max} delayed by 5.5 h	level A
Malcolm *et al.* [19]	8	375	HBS[h] formulation + carbidopa	standard meal	each patient received the same meal	no significant changes in AUC and $t_{1/2}$	level A
Robertson *et al.* [35]	8	125	dissolved in 100 mL of water	high-protein diet	30.5 g of protein	no significant changes in levodopa pharmacokinetics	level B
Robertson *et al.* [35]	8	125	dissolved in 100 mL of water	low-protein diet	10.5 g of protein	↓ AUC by 10%	level B
Hsu *et al.* [115]	4	2000	tablets levodopa alone	pyridoxine	150 mg daily	no significant differences in the excretion of levodopa and its metabolites	level B
Campbell *et al.* [86]	8	250	tablets	ferrous sulfate	325 mg	↓ AUC by 51%, ↓ C_{max} by 55%, no significant changes in $t_{1/2}$[i] and t_{max}	level A

Abbreviations: [a]+ - combined with, [b]↑- an increase, [c]AUC – area under the plasma concentration-time curve, [d]$t_{1/2}$ – half-life time, e↓ - a decrease, [f]Cmax – maximum serum concentration, [g]t_{max} – time to reach maximum serum concentration, [h]HBS - hydrodynamically balanced system

was unaffected; hence both drugs can be safely administered with or without food [110-114].

3.6.2. Tyramine Challenge Studies

Unlike MAO type B, type A enzyme is involved in metabolizing tyramine – a compound present *e.g.* in aged cheese, smoked or processed meat and fish, pickled or fermented foods, and drinks such as wine or tap beer [114]. Inhibition of MAO-A enzyme with the concomitant intake of tyramine-rich foods can result in elevated serum tyramine levels and may lead even to hypertensive crisis, with symptoms such as severe headache, nausea, sweating, fast heartbeat, and shortness of breath. This potentially dangerous reaction is informally called the "cheese effect" [116].

To evaluate MAO inhibitor selectivity, tyramine challenge studies can be performed, with orally or intravenously administered tyramine. Due to the scope of this review, we focused only on studies of orally given tyramine and MAO inhibitors. Results of such studies are usually presented as the tyramine sensitivity factor (TSF) - the ratio of tyramine doses needed to increase systolic BP (*e.g.* by 20, 25, or 30 mmHg) before and after the intake of the investigated drug. TSF higher than 2 is often considered clinically relevant [117].

All MAO inhibitors employed in the treatment of PD are selective for MAO-B if only the indicated therapeutic doses are used, that is: up to 10 mg for selegiline (TSF from 1.75 to 3.12), up to 1 mg for rasagiline (TSF = 2), and up to 100

Table 2. Summary of studies assessing the impact of food on pharmacokinetics and pharmacodynamics of levodopa in parkinsonian patients.

Study	Number of Patients	Patients Characteristics	Mean Drug Dose (mg)	Drug Formulation	Type of Meal / Food Ingredient	Meal / Food Ingredient Characteristics	Observed Effect	Level of Evidence
Nutt *et al.* [17]	9	age: 52-79 disease duration: 8-22 y.[a] mean HY[b]=4 on-off fluctuations	differed among patients	tablets +[c] carbidopa	standard meal	30 ± 14 g of protein, 54 ± 44 g of carbohydrate, 35 ± 18 g of fat	↓[d]AUC[e] by 27%, ↓ C_{max}[f] by 29%, delayed t_{max}[g] by 0.5 h	level B
Baruzzi *et al.* [18]	17	mean age: 65 mean disease duration: 7.4 y. mean HY=2.5	373 ± 169	tablets + carbidopa / benserazide	standard meal, 30 min. before dosing	550 kcal, 48 g of carbohydrates, 36 g of fat, 23 g of protein	↓ AUC by 15%, ↓ C_{max} by 30%, t_{max} delayed by 1.5 h	level B
Malcolm *et al.* [19]	7	age, disease duration and HY not mentioned on-off fluctuations	250	tablets + carbidopa	standard meal	patient's normal diet	↑[i] AUC by 22%	level B
Roos *et al.*[22]	12	mean age: 57.4 disease duration not mentioned mean HY=2.6	200	controlled-release tablets + carbidopa	standard meal	24 g of protein, 2 slices of bread, with cheese and ham and glass (250 ml) of milk	↓ AUC by 14%, ↓ C_{max} by 15%, more flattered levodopa concentration-time profile	level B
Contin *et al.* [23]	8	mean age: 63, mean disease duration: 9.5 y. mean HY=2	200	controlled-release tablets + carbidopa	standard meal, 30 min. before dosing	550 kcal, 48 g of carbohydrates, 36 g of fat, 23 g of protein	↓ AUC by 23%, no significant changes in C_{max}, t_{max} delayed by 1.5 h, significantly delayed time to onset and duration of motor response	level A
Juncos *et al.* [27]	3	mean age: 59 mean disease duration: 14 y. mean HY=4 on-off fluctuations	1.2 ± 0.2 /kg/h	tablets + carbidopa	high-protein formula	0.4 g of protein/kg/day	↑ LNAA[j] levels, prematurely terminated response to levodopa	level B
Frankel *et al.* [28]	4	mean age: 65 mean disease duration: 10 y. mean HY not mentioned on-off fluctuations	50 /h	solution, via the naso-duodenal tube	protein load	60 g of protein	↑ LNAA levels, decline in motor performance despite maintained plasma levodopa levels	level B
Berry *et al.* [29]	9	age, disease duration and HY not mentioned	1000 (600-1750)	tablets + carbidopa	high-protein meal	670 kcal	↑ LNAA levels by 24%, significantly ↑ levodopa plasma levels, worsening of parkinsonian symptoms in 5 patients	level B
Pincus *et al.* [31]	11	mean age: 57 mean disease duration: 12 y. mean HY not mentioned	1259 ± 227 (500–2800)	not mentioned + carbidopa	high-protein diet	160 g of protein/day, milkshakes	persistent bradykinesia	level B
Pincus *et al.* [32]	7	mean age: 56 mean disease duration: 16 y. mean HY not mentioned on-off fluctuations	1243 (400–2800)	tablets + carbidopa	high-protein diet	160 g of protein/day, milkshakes	bradykinesia, ↑ levodopa plasma levels	level B
Pincus *et al.* [33]	15	mean age: 61 mean disease duration: 10 y. mean HY not mentioned on-off fluctuations / non-respondence to levodopa	1182 (450-2000)	tablets + carbidopa	high-protein diet	160 g of protein/day, milkshakes	predominant immobilization, significantly ↑ plasma LNAA levels, and levodopa plasma levels	level B

(Table 2) contd….

Study	Number of Patients	Patients Characteristics	Mean Drug Dose (mg)	Drug Formulation	Type of Meal / Food Ingredient	Meal / Food Ingredient Characteristics	Observed Effect	Level of Evidence
Berry *et al.* [29]	9	age, disease duration and HY not mentioned	1000 (600-1750)	tablets + carbidopa	normal-protein meal	670 kcal	no significant changes in LNAA levels, significantly ↑ levodopa plasma levels, worsening of parkinsonian symptoms in 1 patient	level B
Simon *et al.* [34]	20	mean age: 61 mean disease duration: 9.5 y. mean HY=2.5 on-off fluctuations / dyskinesias	213.7 ± 93.7 / intake	differed among patients + carbidopa	low-protein meal (A) *vs.* high-protein meal (B)	(A): 411 kcal, 7.6 g of protein, (B): 885 kcal, 38.7 g of protein	after (B) - no significant differences in C_{max} and t_{max}, AUC ↑ by 47% relative to the (A)	level B
Gillespie *et al.* [36]	8	age, disease duration and HY not mentioned	not mentioned	not mentioned	low-protein diet	0.5 g/kg/day, in 6 meals	more potent and stable levodopa mode of action	level B
Tsui *et al.* [38]	10	mean age: 64 mean disease duration: 12.4 y. mean HY not mentioned	535 (300–875)	not mentioned, + carbidopa	low-protein diet (A) *vs.* high-protein diet (B)	(A): 0.7 g/kg/day, (B): 1.1-1.2 g/kg/day	(A): ↑ "on" time by 1 h per day, improved parkinsonian symptoms, and ↓ plasma levodopa levels relative to (B)	level A
Carter *et al.* [39]	5	mean age: 65.2 mean disease duration: 19.4 y. mean HY not mentioned	1560 ± 619 (700–2400)	not mentioned + carbidopa	low-protein diet (A) *vs.* high-protein diet (B)	(A): 7 g of protein/day (0.8 g/kg/day), (B): 1.6 g/kg/day	(A): ↑ "on" time by 4.2 h per day and ↓ plasma LNAA levels relative to (B)	level B
Barichella *et al.* [40]	18	mean age: 60.6 mean disease duration: 11.5 y. mean HY=2.6 on-off fluctuations	567.5 ± 226.4	not mentioned	LPP[k] (A) *vs.* balanced diet (B)	0.8 g of protein/kg/day (A): 85.3% at dinner (B): 39.8% at dinner	↓ "off" phases by 40% and ↓ total "off" time by 1.8 h/day, relative to (B)	level A
Juncos *et al.* [27]	6	mean age: 59 mean disease duration: 14 y. mean HY=4 on-off fluctuations	1.2 ± 0.2 /kg/h	tablets + carbidopa	low-protein meals	0,78 g of protein/kg/day 3 x meal (A): 0.26 g of protein/kg/meal, 12% of protein, 42% of carbohydrate, 46% of fat; or 6 x meal (B): 0.13 g of protein/kg/meal, 14% of protein, 54% of carbohydrate, 32% of fat	no significant changes in LNAA levels and response to levodopa relative to the fasting state for both meals	level B
Berry *et al.* [29]	9	age, disease duration and HY not mentioned	1000 (600-1750)	tablets + carbidopa	low-protein, high-carbohydrate meal	670 kcal	LNAA levels ↓ by 18%, significantly ↑ levodopa plasma levels, worsening of parkinsonian symptoms in 3 patients	level B
Mena *et al.* [30]	8	age, disease duration and HY not mentioned	1800-8000	not mentioned +/- carbidopa	low-protein diet	0.5 g of protein/kg/day	↓ disability score by 3.4 points	level B
Barichella *et al.* [41]	6	mean age: 66 mean disease duration: 18 y. mean HY not mentioned on-off fluctuations	579 ± 293	not mentioned	LPP (A) *vs.* low-protein diet (B)	0.8–1 g of protein/kg/day, (A): 87.3% at dinner, with LPP, (B): 64.1% at dinner, without LPP	↑ mean "on" time by 1.5 h, ↓ mean "off" time by 1.5 h	level A

(Table 2) contd….

Study	Number of Patients	Patients Characteristics	Mean Drug Dose (mg)	Drug Formulation	Type of Meal / Food Ingredient	Meal / Food Ingredient Characteristics	Observed Effect	Level of Evidence
Pincus *et al.* [31]	11	mean age: 57 mean disease duration: 12 y. mean HY not mentioned	1259 ± 227 (500–2800)	not mentioned + carbidopa	protein redistribution diet	7 g of protein/day (0.8 g/kg/day), before the evening meal	marked relief of parkinsonian symptoms and ↓ severity of motor fluctuations in 9 patients, mean levodopa daily dose ↓ by 42% in 8 patients	level B
Pincus *et al.* [33]	8	mean age: 56 mean disease duration: 12 y. mean HY not mentioned on-off fluctuations	1497 (575-2000)	tablets + carbidopa	protein redistribution diet	7 g of protein/day (0.8 g/kg/day), before the evening meal	immediate clinical benefit in 7 patients, mean levodopa daily dose ↓ by 42% in 6 patients	level B
Pincus *et al.* [33]	7	mean age: 66 mean disease duration: 8 y. mean HY not mentioned non-respondence to levodopa	866 (450-1750)	tablets + carbidopa	protein redistribution diet	7 g of protein/day (0.8 g/kg/day), before the evening meal	immediate sensitivity to levodopa in 6 patients	level B
Pincus *et al.* [32]	7	mean age: 56 mean disease duration: 16 y. mean HY not mentioned on-off fluctuations	1243 (400–2800)	tablets + carbidopa	protein redistribution diet	1600 kcal, 7 g of protein, in 2 meals	levodopa-induced dyskinesia, mean levodopa daily dose ↓ by 28% in 5 patients	level B
Gillespie *et al.* [36]	8	age, disease duration and HY not mentioned	not mentioned	not mentioned	protein redistribution diet	10 g of protein/day, in 3 meals	more potent and stable levodopa mode of action	level B
Pincus *et al.* [43]	8	mean age: 68 mean disease duration: 8 y. mean HY not mentioned on-off fluctuations	1054 ± 153	tablets + carbidopa	protein redistribution diet	7 g of protein per day (0.8 g/kg/day), before the evening meal	restored sensitivity to levodopa in 14 patients, disability score ↓ by 16 points	level B
Riley *et al.* [44]	30	mean age: 61 mean disease duration: 14 y. mean HY not mentioned on-off fluctuations	885 (200–1700)	tablets + carbidopa	protein redistribution diet	7 g of protein per day (0.8 g/kg/day), before the evening meal	↓ "off" time by 3.5 h per day in 14 patients, improved motor performance in 8 patients	level B
Bracco *et al.* [45]	16	mean age: 65 mean disease duration: 9 y. mean HY=3	625 (375–1000)	tablets + carbidopa	protein redistribution diet	0.8 g of protein/kg/day (10% protein, 30% fat, 55% carbohydrates), before the evening meal	↓ total disability score by 11 points, ↓ bradykinesia, ↓ rigidity, ↓ tremor, more constant response to levodopa	level B
Karstaedt *et al.* [46]	43	mean age: 69 mean disease duration: 13.7 y. mean HY not mentioned on-off fluctuations	840	not mentioned + carbidopa	protein redistribution diet	7 g of protein/day (0.8 g/kg/day), before the evening meal	↑ mean "on" time by 59%, ↓ total disability score by 12.7 points	level C
Giménez-Roldán *et al.* [47]	15	mean age: 64.7 mean disease duration: 9.6 y. mean HY not mentioned on-off fluctuations	906 (312–2000)	not mentioned + carbidopa	protein redistribution diet	2000-2500 kcal, 65-80 g of protein/day	↓ mean "off" time by 79% in 10 patients	level B
Virmani *et al.* [48]	877	mean age: 60 mean disease duration: 9 y. mean HY not mentioned	not mentioned	differed among patients + carbidopa	dietary protein	not mentioned	motor fluctuations due to the protein interaction in 52 (5.9%) patients: earlier onset of motor symptoms, decreased efficacy of levodopa (26/52), dose failures (9/52), sudden "off" phases (15/52)	level C

(Table 2) contd….

Study	Number of Patients	Patients Characteristics	Mean Drug Dose (mg)	Drug Formulation	Type of Meal / Food Ingredient	Meal / Food Ingredient Characteristics	Observed Effect	Level of Evidence
Gordon *et al.* [50]	1	age: 43 disease duration: 10 y. HY not mentioned	900	crushed tablets	enteral nutrition	not mentioned	development of neuroleptic malignant–like syndrome	level D
Cooper *et al.* [51]	1	age: 77 disease duration and HY not mentioned	600	crushed tablets + carbidopa	enteral nutrition	1.4 g of protein/kg/day	severe rigidity despite the treatment	level D
Bonnici *et al.* [52]	1	age: 63 disease duration not mentioned HY=2	600	crushed tablets + carbidopa	enteral nutrition	switch from 0.88 to 1.8 g of protein/kg/day	development of neuroleptic malignant–like syndrome	level D
Shoulson *et al.* [57]	4	mean age: 56 mean disease duration: 6 y. HY not mentioned	1050-2275	tablets + carbidopa	caffeine	gradually increasing daily dose, from 300 to 1400 mg	no significant changes in parkinsonian severity, 26% ↑ in the duration of involuntary movements	level B
Nicoletti *et al.* [58]	485	mean age: 65, disease duration variable mean HY=2.5	435 ± 230 - 719 ±324	not mentioned	coffee	from 0 to > 3 cups of coffee per day, depending on a patient	a negative association between the presence of LID[!] and coffee drinking, ↓ risk of LID with ↑ number of cups per day	level C
Deleu *et al.* [60]	12	mean age: 61 mean disease duration: 6.3 y. mean HY=2	250	tablets + carbidopa	caffeine	200 mg	↓ t_{max} (by 0.5 h), comparable C_{max} and AUC,↓ latency to levodopa walking and tapping response (2 and 3 times, respectively), 44% ↑ magnitude of walking response	level A
Fernandez-Martinez *et al.* [66]	18	mean age: 70 mean disease duration: 1.3 y. mean HY not mentioned	300	tablets + carbidopa	fiber	*Plantago ovata* husk, 3.5 g	↓ number of peaks in levodopa concentrations - more stable absorption, no significant changes in AUC and C_{max}	level A
Astarloa *et al.* [67]	19	mean age: 67.3 mean disease duration: 6.5 y. mean HY=2.35	525 ± 48	not mentioned	fiber	a diet rich in fiber (28 g of highly insoluble fiber daily)	71% ↑ levodopa bioavailability, significant improvement in motor function	level B
Nagayama *et al.* [70]	67	mean age: 77.8 mean disease duration: 4.1 y. mean HY=3.1	100	tablets + carbidopa	vitamin C	200 mg	↑ AUC by 35%, ↑ C_{max} by 53%, ↓ t_{max} by 38% (but only in 25 patients with poor levodopa bioavailability)	level B
Golden *et al.* [71]	1	age: 76 disease duration and HY not mentioned	700	tablets levodopa alone	pyridoxine	not applicable	burning feet syndrome, probably due to the levodopa-induced pyridoxine deficiency	level D
Yahr *et al.* [72]	1	age: 55 disease duration and HY not mentioned	4500	tablets levodopa alone	pyridoxine	100 mg daily	reduction of levodopa-induced dyskinesia but with the reoccurrence of parkinsonism symptoms	level D
Leon *et al.* [73]	4, with PD	mean age: 62.5 disease duration not mentioned mean HY=2.25,	3500-6000	tablets levodopa alone	pyridoxine	50 mg daily	60% ↓ levodopa plasma levels, ↓ excretion of levodopa and dopamine, exacerbation of parkinsonian symptoms in 3 patients	level B
Mars *et al.* [75]	10, with PD	age, disease duration and HY not mentioned	250	tablets levodopa alone	pyridoxine	50 mg	67% ↓ levodopa plasma levels, 49% ↑ of levodopa metabolite - homovanillic acid level, significantly ↑ decarboxylation index	level B

(Table 2) contd….

Study	Number of Patients	Patients Characteristics	Mean Drug Dose (mg)	Drug Formulation	Type of Meal / Food Ingredient	Meal / Food Ingredient Characteristics	Observed Effect	Level of Evidence
Mars *et al.* [75]	10	age, disease duration and HY not mentioned	250	tablets + carbidopa	pyridoxine	50 mg	no significant changes in levodopa plasma levels and homovanillic acid levels, significantly ↓ decarboxylation index	level B
Cotzias *et al.* [77]	7	age, disease duration and HY not mentioned	differed among patients	tablets + carbidopa	pyridoxine	100 mg daily	no significant increases in neurological signs	level B
Papavasiliou *et al.* [78]	14	age, disease duration and HY not mentioned	differed among patients	tablets + carbidopa	pyridoxine	300-600 mg daily	no significant increases in neurological signs	level B
Klawans *et al.* [79]	7	mean age: 57 mean disease duration: 7 y. mean HY=3	1700	tablets + carbidopa	pyridoxine	100 mg daily	no significant increases in disability or physical status	level B
Rojo *et al.* [80]	18	mean age: 73 mean disease duration: 13 y. mean HY=3.1	875	tablets + carbidopa	pyridoxine	not applicable	pyridoxine deficiency in 13 patients chronically treated with levodopa	level D
Loens *et al.* [82]	13	mean age: 72.8 mean disease duration: 13.7 y. mean HY=4	865.8 ± 567	tablets + carbidopa	pyridoxine	not applicable	↓ pyridoxine level with the ↑ daily levodopa dose, neuropathy in 8 patients	level C
Hsu *et al.* [115]	5	age 57-76 mean disease duration and HY not mentioned	2000	tablets levodopa alone	pyridoxine	150 mg daily	↓ excretion of levodopa, ↑ excretion of levodopa metabolites, suggesting enhanced extracerebral levodopa metabolism	level B
Campbell *et al.* [87]	9	mean age: 56.5 mean disease duration and HY not mentioned	200-800	tablet + carbidopa	ferrous sulfate	325 mg	↓ AUC by 30%, ↓ C_{max} by 47%, no significant changes in $t_{1/2}$[m] and t_{max}	level A
Karstaedt *et al.* [90]	18	mean age: 65.4 mean disease duration: 11.9 y. HY not mentioned	differed among patients	tablets + carbidopa	aspartame	600 mg or 1200 mg	no changes in motor performance	level B

Abbreviations: [a]y. – years, [b]HY - Hoehn and Yahr scale, [c]+ - combined with, [d]PD – Parkinson's disease, [e]↓ - a decrease, [f]AUC – area under the plasma concentration-time curve, [g]C_{max} – maximum serum concentration, [h]t_{max} – time to reach maximum serum concentration, [i]↑ - an increase, [j]LNAA - large neutral amino acids, [k]LPP – low protein products, [l]LID-levodopa-induced dyskinesias, [m]$t_{1/2}$ – half-life time

mg for safinamide (TSF = 2.15) [117-123]. However, with the increasing dose, MAO-B inhibitors may lose their selectivity and bind to MAO-A as well [124]. In consequence, higher TSF can be observed, especially for selegiline (20-60 mg doses – TSF from 1.42 to 4), and for rasagiline (2-6 mg doses – TSF from 2.4 to 5.1) [119, 120, 123, 125]. Additionally, in two studies of selegiline in doses 20-30 mg, symptoms of "cheese effect" were reported, such as headache with marked elevation of blood pressure, palpitations, and nausea [125, 126]. Safinamide seems to be the most selective of investigated MAO-B inhibitors – no significant changes in TSF were reported even for supratherapeutic doses (300-350 mg) [121, 127].

It is not necessary to recommend dietary tyramine restriction to all PD patients treated with MAO-B inhibitors. If doses higher than 10 mg/day of selegiline or 2 mg/day of rasagiline are required, *e.g.* to treat concomitant depression, patients should be advised to limit the amount of tyramine-rich products consumption [120, 125]. However, in patients with advanced PD – who can have difficulties in maintaining tyramine-restricted diet or might incidentally ingest higher drug dose than prescribed - changing selegiline formulation from oral to transdermal would be a better alternative [124].

3.7. Anticholinergic Drugs

Anticholinergic drugs (syn. cholinolytics), *e.g.*, biperiden, benztropine, pridinol or trihexyphenidyl, act by blocking the action of acetylcholine – the neurotransmitter involved in movements regulation. Adding cholinolytics to PD therapy can help ease the tremor, dystonia and excessive salivation. However, anticholinergic drugs are potentially inappropriate in elderly, due to adverse effects such as cognitive slowing, confusion, blurred vision, and constipation [13].

Data of the food effect on pharmacokinetics and pharmacodynamics of anticholinergic drugs are scarce. We found

Table 3. Summary of studies assessing the impact of food on pharmacokinetics and pharmacodynamics of dopamine agonists.

Drug	Study	Number of participants	Participants characteristics	Mean drug dose (mg)	Drug formulation	Type of meal / food ingredient	Meal / food ingredient characteristics	Observed effect	Level of evidence
Cabergoline	Persiani *et al.* [91]	12	healthy	1	tablets	standard meal, concomitantly with dosing	41 g of carbohydrates, 82.3 g of fat, and 43 g of protein	no significant changes in AUC[a], C_{max}[b], and t_{max}[c]	level A
Ropinirole	Brefel *et al.* [92]	12	with PD[d] mean age: 62 mean disease duration and HY[e] not mentioned	6	tablets	high-fat meal	927 kcal; 58 g of carbohydrates (24%), 64 g of fat (61%) and 33 g of protein (14%)	↓[f] AUC by 11%, ↓ C_{max} by 25%, t_{max} delayed by 2.6 h	level A
-	Tompson *et al.* [93]	21	with PD mean age: 67 mean disease duration not mentioned HY=1-3	8	prolonged-release tablets	high-fat meal, 30 min before dosing	as defined by the US FDA	no significant changes in AUC_{0-24}, ↑[g] C_{max} by 15%, t_{max} delayed by 2 h	level A
-	Hattori *et al.* [94]	10	with PD mean age: 20 and older mean disease duration not mentioned HY=2	8-16	prolonged-release tablets	standard meal	500 kcal	no significant changes in steady-state AUC_{0-24}, C_{max}, C_{min}[h], t_{max}	level B
Bromocriptine	Drewe *et al.* [95]	8	healthy	5	modified-release capsules *vs.* standard capsules	standard meal, 10 min before dosing	150 mL of orange juice, 2 rolls, 20 g of butter, 25 g of marmalade, 2 scrambled eggs, 2 slices of bacon, and 200 mL whole milk	modified-release capsules: delayed t_{lag}[i] by 1 h, no significant changes in other parameters standard capsules: ↓ C_{max} by 48%, no significant changes in other parameters	level B
-	Kopitar *et al.* [96]	7	healthy	7.5	tablets	standard meal	carbohydrates (33%), fat (8%), protein (23%), other (36%)	↓ C_{max} by 18%, no significant changes in other parameters	level B

Abbreviations: [a]AUC – area under the plasma concentration-time curve, [b]C_{max} – maximum serum concentration, [c]t_{max} – time to reach maximum serum concentration, [d]PD – Parkinson's disease, [e]HY - Hoehn and Yahr scale, [f]↓ - a decrease, [g]↑ - an increase, [h]C_{min} – minimum serum concentration, [i]t_{lag} – lag time, time taken for a drug to appear in systemic circulation

Table 4. Summary of studies assessing the impact of food on pharmacokinetics and pharmacodynamics of COMT inhibitors, MAO-B inhibitors, amantadine, and pimavanserin.

Drug	Study	Number of Participants	Participants Characteristics	Mean Drug Daily Dose (mg)	Drug Formulation	Type of Food/Dietary Ingredient	Food Characteristics	Observed Effect	Level of Evidence
Opicapone	Almeida *et al.* [103]	12	healthy	50	capsules	high-fat meal, 30 min before dosing	240 mL of whole milk, 2 eggs fried in butter, 4 oz of hash brown potatoes, 1 English muffin with 11 g of butter, and 2 strips of bacon	↓[a] AUC[b] by 51%,↓ C_{max}[c] by 63%, $t_{1/2}$[d] delayed by 2.2 h	level A
-	Santos *et al.* [104]	12	healthy	50	not mentioned	high-fat meal	not mentioned	↓ AUC by 53%↓ C_{max} by 68%, delayed t_{max}[e]	level B
-	Santos *et al.* [104]	28	healthy	50	not mentioned	moderate-fat meal	not mentioned	↓ AUC by 31%↓ C_{max} by 62%, delayed t_{max}	level B
Selegiline	Barrett *et al.* [107]	11	healthy	10	tablets	high-fat meal, immediately after dosing	-	↑[f] AUC by 369%, ↑ C_{max} by 228%, ↓ t_{max} by 1 h, no significant changes in selegiline metabolites levels	level A
-	Elsworth *et al.* [118]	4 + 6	healthy + with PD[g] age: 38-72 disease duration and HY[h] not mentioned	up to 10	not mentioned	tyramine	from 6.25 up to 400 mg	no adverse pressor reaction ("cheese effect")	level B
-	Clarke *et al.* [133]	24	healthy	1.25 (1) *vs.* 10 (2)	orally disintegrating tablets (1) *vs.* tablets (2)	tyramine	baseline PD50[i] = 400 mg	after 4 weeks of selegiline intake: (1) no significant changes in PD50 (2) PD50 = 200 mg	level A
-	Haffner *et al.* [117]	59	healthy	10	not mentioned	tyramine	from 75 up to max. 800 mg	TSF[j] = 1.83	level A
-	Stern *et al.* [119]	4	with PD age, disease duration and HY not mentioned	10	not mentioned	tyramine	from 6.25 up to max. 400 mg	TSF = 1.75	level B
-	Simpson *et al.* [134]	10	with PD age, disease duration and HY not mentioned	10	not mentioned	tyramine	up to max. 400 mg	slightly ↑ sensitivity to oral tyramine	level B
-	Goren *et al.* [120]	15	healthy	10	not mentioned	tyramine	from 12.5 up to max. 500 mg	TSF = 2.5	level A
-	Marquet *et al.* [121]	18	healthy	10	tablets	tyramine	from 25 up to max. 700 mg	TSF = 3.12	level A
-	Schulz *et al.* [123]	8	healthy	5 (1) *vs.* 20 (2)	tablets	tyramine	-	(1) TSF = 1.7, (2) TSF = 3.8	level B

(Table 4) contd….

Drug	Study	Number of Participants	Participants Characteristics	Mean Drug Daily Dose (mg)	Drug Formulation	Type of Food/Dietary Ingredient	Food Characteristics	Observed Effect	Level of Evidence
-	McGrath *et al.* [126]	1	with PD age, disease duration and HY not mentioned	20	tablets	tyramine	macaroni cheese	"cheese effect" - headache with marked elevation of blood pressure	level D
-	Prasad *et al.* [125]	8	healthy	30	not mentioned	tyramine	from 12.5 up to max. 400 mg	TSF = 2-4 (↑ systolic and diastolic blood pressure, headache, palpitations, nausea)	level B
-	Stern *et al.*[119]	4	with PD age, disease duration and HY not mentioned	40-60	not mentioned	tyramine	from 6.25 up to max. 400 mg	TSF = 1.42	level B
Rasagiline	Gu *et al.* [110]	12	healthy	1	tablets	high-fat meal	not mentioned	no significant changes in AUC, ↓ C_{max} by 60%, delayed t_{max} by 25 min.	level A
-	Li *et al.* [111]	108	healthy	1	tablets	high-fat meal	1000 kcal, 60% of fat, 15% of protein, 25% of carbohydrates	slightly ↓ AUC by 19%, ↓ C_{max} by 51%, delayed t_{max} by 40 min.	level A
-	deMarcaida *et al.* [122]	110	with PD mean age: 62.5 mean disease duration: 5.3 y. mean HY not mentioned	0.5-2	tablets	tyramine	50-75	no clinically significant tyramine reactions, self-limiting systolic blood pressure elevations of more than 30 mm Hg in 3 patients	level A
-	Goren *et al.* [120]	77	healthy	1-6	not mentioned	tyramine	from 12.5 up to max. 500 mg	TSF for 1 mg = 2, TSF for 2 mg = 2.4-3.3, TSF for 4 mg = 4.5, TSF for 6 mg = 5.1	level A
Safinamide	Marzo *et al.* [112]	6	healthy	0,9/kg	not mentioned	high-fat meal	1000 kcal, 1 buttered muffin (fat = 9.2 g), 1 fried egg (fat = 10.0 g), 30 g of cheese (fat = 10.2 g), 1 piece of bacon (fat = 4.0 g), 1 serving of boiled potatoes (fat = 9.6 g), 250 mL of whole milk (fat = 8.25 g)	no significant changes in AUC, ↓ C_{max} by 16%, delayed t_{max} by 3.3 h	level A
-	Seithel-Keuth *et al.* [113]	14	healthy	50	tablets	high-fat meal	800–1000 calories, 50% of fat	no significant changes in AUC and C_{max}, delayed t_{max} by 0.75 h	level A
-	Di Stefano *et al.* [127]	20	healthy	300	capsules	tyramine	from 50 up to max. 200 mg	no systolic blood pressure increases ≥ 30 mmHg over baseline	level B

(Table 4) contd….

Drug	Study	Number of Participants	Participants Characteristics	Mean Drug Daily Dose (mg)	Drug Formulation	Type of Food/Dietary Ingredient	Food Characteristics	Observed Effect	Level of Evidence
-	Marquet *et al.* [121]	36	healthy	100 *vs.* 350	tablets	tyramine	from 25 up to max. 700 mg	TSF for 100 mg = 2.15, TSF for 350 mg = 2.74 (TSF for placebo = 1.52)	level A
Amantadine	deVries *et al.* [131]	24	healthy	258	extended-release tablets	high-fat meal	not mentioned	no significant changes in AUC, $C_{max,}$ and t_{max}	level A
Pimavanserin	Vanover *et al.* [132]	8	healthy	100	tablets	high-fat meal	2 eggs fried in butter, 2 strips of bacon, 2 pieces of buttered toast, 4 oz of hash brown potatoes, and 8 oz of whole milk; 55 g of fat, 33 g of protein, and 58 g of carbohydrates	no significant changes in AUC and C_{max}, delayed t_{max} by 4.5 h	level A

Abbreviations: [a]↓ - a decrease, [b]AUC – area under the plasma concentration-time curve, [c]C_{max} – maximum serum concentration, [d]$t_{1/2}$ – half-life time, [e]t_{max} – time to reach maximum serum concentration, [f]↑ - an increase, [g]PD – Parkinson's disease, [h]HY - Hoehn and Yahr scale, [i]PD50- oral tyramine dose at which 50% of subjects reached the threshold pressor response, [j]TSF – tyramine sensitivity factor

evidence for the negative interaction between cholinolytics and potassium chloride (KCl). Enteric-coated or delayed-release KCl formulations have the potential to irritate esophageal and gastric mucosa. This effect is intensified in the presence of drugs that delay gastric emptying, such as cholinolytics [128]. In a retrospective study of almost 14.000 patients treated with KCl, 0.2% experienced upper gastrointestinal bleeding events. In patients concomitantly treated with anticholinergic drug, the rate of upper gastrointestinal bleeding events was significantly higher than in those without exposure to cholinolytics (0.3% *vs.* 0.1%) [129]. Based on this results, co-intake of anticholinergic drugs and potassium chloride should be avoided.

3.8. Amantadine

Amantadine is available in immediate-release (IR) tablets, capsules, syrup, and extended-release (ER) tablets. Both IR and ER formulations can be used as the combined treatment with levodopa – to reduce dyskinesia and wearing off [130]. Additionally, IR formulations are registered for monotherapy – to mildly improve motor symptoms in patients with early PD. We found only one study investigating the influence of a high-fat meal on pharmacokinetic parameters of ER amantadine tablets. In this trial, no significant changes in AUC, C_{max}, and t_{max} occurred [131]. Based on available data, all amantadine formulations can be ingested irrespective of food.

3.9. Pimavanserin

A second-generation antipsychotic drug, pimavanserin, is also applied in PD patients to treat PD-related psychosis [10]. In a food effect study, the presence of high-fat meals significantly delayed pimavanserin tablets t_{max} (by 4.5 h), possibly due to the slower gastric emptying. Nevertheless, both AUC and C_{max} were unaffected; hence pimavanserin can be administered with or without meals [132].

In Table **4**, we present detailed characteristics of studies assessing the impact of food on pharmacokinetics and pharmacodynamics of COMT inhibitors, MAO-B inhibitors, amantadine, and pimavanserin.

3.10. Studies Limitations

We can point out several limitations of the studies included in this systematic review:

- presence of older studies – the majority of food-effect studies, especially for levodopa, were performed earlier than in the previous 20 years (in 70s, 80s or 90s),
- missing data – not in every study following information were mentioned: patients characteristics (age, disease duration, HY stage of disease), drug dose or formulation, meal composition, dietary supplement dose,
- disproportionate evidence - more than half of the studies applied to levodopa, only single or no studies were available for other groups of antiparkinsonian drugs,
- low level of evidence – more than half of studies were assigned as level B or lower, and included a small number of patients.

CONCLUSION

Elderly patients with advanced Parkinson's disease are at the highest risk of medication-related adverse events, as well as the drug-drug, and drug-food interactions. It is principally due to polypharmacy, self-medication with OTC drugs and dietary supplements, together with poor compliance and age-related changes in pharmacokinetics and pharmacodynamics [13]. Pharmacokinetic changes that may influence PD thera-

py are *e.g.*, increased gastric pH, delayed gastric emptying, increased permeability of the blood brain barrier, decreased both hepatic metabolism, and elimination processes [135]. Of pharmacodynamic changes, deficiency of dopamine transporters and uptake sites should be noted, with concomitant increased sensitivity to dopamine [136]. However, not only patient-related problems, but also the lack of causative treatment and varied responses to drugs make PD therapy extremely challenging. The proper intake of drugs regarding meals and avoiding drug-nutrients interactions may help to optimize the PD therapy; hence, in this systematic review, we provided and discussed the available evidence in that matter.

For levodopa, the problem of drug-nutrients interaction was widely investigated. Nevertheless, the overall level of evidence is low due to the poor studies design (mainly non-randomized or without the control group) and their low actuality. We found evidence for levodopa positive interaction with coffee, fiber and vitamin C, as well as for the potential beneficial impact of low-fat and protein redistribution diet. Contrastingly, high-protein diet and ferrous sulfate supplements can negatively affect levodopa bioavailability and effectiveness. Various levodopa formulations are differently affected by food: immediate-release and dispersible tablets should be taken on an empty stomach, while modified-release forms can be administered irrespectively of meals.

For other antiparkinsonian drugs, the data of food impact are scarce. Based on available limited evidence, all dopamine agonists (bromocriptine, cabergoline, ropinirole), tolcapone, rasagiline, safinamide, amantadine and pimavanserin can be taken with or without meal. Opicapone should be administered on an empty stomach. The impact of food on selegiline absorption depends on drug formulation: tablets should be co-administered with food; whether orally disintegrating tablets need to be taken 5 minutes before or after the meal. Of MAO-B inhibitors, safinamide is the least susceptible for interaction with the tyramine-rich food, whereas selegiline and rasagiline may lose their selectivity to MAO-B when administered in supratherapeutic doses. However, introducing tyramine-restricted diet is not necessary if standard doses of MAO-B inhibitors are applied.

Our review reveals existing gaps of knowledge in the topic of PD drugs-nutrients interactions and highlights the need for further investigation, with the aim to optimize the effectiveness of treatment and to improve the safety of patients. It is particularly important in the context of demographic changes, predicted increase of PD incidence, and the prevalence of drug-induced parkinsonism.

AUTHORS' CONTRIBUTIONS

A.W.: searching and selecting the literature, extracting the evidence, summarizing, and presenting the data; writing manuscript; P.P.: conceptualization, supervision M.K.: conceptualization, planning, supervision.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines were followed for the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

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